SPECIFICATION

Agent for Modulating Growth or Generation of Hair

Technical Field

The present invention relates to an agent for modulating growth or generation of hair, which promotes or inhibits growth or generation of hair.

Background Art

Each hair has its own growth cycle (anagen, catagen, telogen and defluxion). However, when generation or growth cycle of each hair is disturbed by a genetic cause or by some other cause, the hair rapidly falls out or conversely grows lengthily and thickly. Abnormal generation of hair includes atrichia and hirsutism, and abnormal hair growth includes alopecia (male pattern alopecia and alopecia areata). These causes are thought to include various factors such as influences by hormones, decrease in blood flow into, hair follicle hypersteatosis, unbalanced diet and stress. Thus, conventional therapy is performed by reducing these causes. For example, therapies of alopecia include inhibition of androgen, increasing in blood flow into hair follicle, pharmacotherapies using compounds which remove unnecessary cuticle and sebum, dietetic treatment and psychotherapies. Since the real cause of alopecia has not been completely clarified, sufficient therapeutic or preventive effect has not been attained. Methods for removing hairs such as body hairs include physical treatments using shavers or depilators, and pharmacotherapies using grainer creams or depilatory creams. However, these methods accompany skin chapping or irritation pain, so that they are not satisfactory as depiliation methods. Thus, development of an agent for modulating growth or generation of hair, which shows sufficient effect, has been demanded for a long time.

It has been disclosed that E type prostaglandins (hereinafter referred to as "PG" for short) and their derivatives promote growth of hair (WO9833497). However, prostaglandin E_2 (hereinafter referred to as "PGE_2" for short) shows a wide

variety of physiological actions such as uterine-contracting action, gastric acid secretion-inhibiting action, gastric mucosa-protecting action, stimulation action of peristalsis of digestive tract, febrifacient action and diarrhea-causing action. Therefore, if PGE_2 is used for the purpose of growing or generating hair, these actions act as side effects.

physiological actions by PGE_2 are expressed by binding of PGE_2 to specific receptors. Further, the receptors to which PGE_2 bind may be classified into 4 receptor subtypes called EP1, EP2, EP3 and EP4 receptors (Coleman,R.A.et al., Pharmacol. Rev.,46,205-229(1994)). It is also known that each receptor subtype participates in different physiological action. For example, the febrile response by PGE_2 is caused by binding of PGE_2 to EP3 receptor (Ushikubi F., Nature, 395, 281-284 (1998)). It is known that compounds which specifically bind to EP4 receptor subtype are effective for prevention, therapy or amelioration of immune diseases, asthma, osteodystrophy, apoptosis of neurocytes, hepatopathy, nephritis, hypertension, myocardial ischemia, gastrointestinal disorder, shock and the like (Japanese Laid-open Patent Application (Kokai) No. 10-265454, WO98/55468). However, it is not known that these compounds have hair generation- or hair growth-modulating actions.

Disclosure of the Invention

An object of the present invention is to provide an agent for modulating growth or generation of hair, which has an excellent activity for modulating growth or generation of hair, and of which side effect is small.

The present inventors intensively searched the compounds which have small side effects and which show excellent activities for modulating growth or generation of hair to discover that compounds which strongly act on EP4 receptor and which weakly bind to other subtypes of PGE_2 attain this object, thereby completing the present invention.

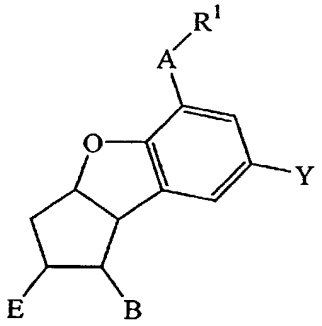
That is, the present invention provides an agent for modulating growth or

generation of hair comprising a prostaglandin EP4 receptor ligand as an active ingredient. The present invention also provides use of a prostaglandin EP4 receptor ligand for production of an agent for modulating growth or generation of hair. The present invention further provides a method for modulating growth or generation of hair comprising administering a prostaglandin EP4 receptor ligand in an amount effective for modulating growth or generation of hair to human or an animal.

The agent for modulating growth or generation of hair according to the present invention has an excellent activity for modulating growth or generation of hair, and its side effects are small.

Best Mode for Carrying Out the Invention

The prostaglandin EP4 receptor ligand is not restricted as long as it acts on prostaglandin EP4 receptor. Examples of such a ligand include 5,6,7-trinor-4,8-inter-m-phenylene PGI_2 derivatives of the following Formula (I) and pharmacologically acceptable salts thereof:

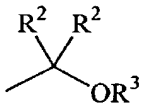


(I)

[wherein

R^1 is

(i)



wherein R^2 is hydrogen, C_1-C_4 linear alkyl, C_3 or C_4 branched alkyl, trifluoromethyl, -C(=O)-R^4, or -C(=O)-O-R^4, wherein R^4 is C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, C_3-C_{12} cycloalkyl, C_7-C_{12} aralkyl, phenyl or substituted phenyl (wherein the substituent is at least one fluorine, chlorine, bromine, iodine, trifluoromethyl, C_1-C_4 alkyl, nitro, cyano, methoxy, phenyl, phenoxy, p-acetamidebenzamide, -CH=N-NH-C(=O)-NH_2, -NH-C(=O)-Ph, -NH-C(=O)-CH_3 or -NH-C(=O)-NH_2), and the two R^2s may be the same or different; R^3 is hydrogen, C_1-C_4 alkyl, C_1-C_{12} acyl, C_7-C_{16} aroyl, C_7-C_{16} aralkyl, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl, allyl, tert-butyl or tert-butyldimethylsilyl,

(ii) -$COOR^5$

wherein R^5 is

(1) hydrogen or pharmacologically acceptable cation,

(2) C_1-C_{12} linear alkyl or C_3-C_{14} branched alkyl,

(3) -Z-R^6

wherein Z is a valence bond, or linear or branched alkylene represented by the formula C_tH_{2t} wherein t represents an integer of 1 to 6, R^6 is C_3-C_{12} cycloalkyl, or C_3-C_{12} cycloalkyl substituted with 1 to 4 R^7s wherein R^7 is hydrogen or C_1-C_5 alkyl,

(4) -$(CH_2CH_2O)_nCH_3$

wherein n represents an integer of 1 to 5,

(5) -Z-Ar

wherein Z is defined as the same as the above, Ar is phenyl, α-naphthyl, β-naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, α-furyl, β-furyl, α-thienyl, β-thienyl or substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above),

(6) -$C_tH_{2t}COOR^8$

wherein t is defined as the same as the above, R^8 is hydrogen or C_1-C_5 alkyl,

(7) $-C_tH_{2t}N(R^9)_2$

wherein t is defined as the same as above, R^9 is hydrogen or C_1-C_5 alkyl, and the two R^9s may be the same or different,

(8) $-CH(R^{10})-C(=O)-R^{11}$

wherein R^{10} is hydrogen or benzoyl, R^{11} is phenyl, p-bromophenyl, p-chlorophenyl, p-biphenyl, p-nitrophenyl, p-benzamidephenyl or 2-naphthyl,

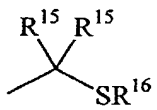
(9) $-C_pH_{2p}-W-R^{12}$

wherein p represents an integer of 1 to 5, W is -CH=CH-, $-CH=C(R^{13})-$ or $-C\equiv C-$ wherein R^{13} is C_1-C_{30} linear alkyl, C_3-C_{30} branched alkyl or C_7-C_{30} aralkyl, R^{12} is hydrogen, C_1-C_{30} linear alkyl, C_3-C_{30} branched alkyl or C_7-C_{30} aralkyl, or

(10) $-CH(CH_2OR^{14})_2$

wherein R^{14} is C_1-C_{30} alkyl or C_1-C_{30} acyl, and the two R^{14}s may be the same or different,

(iii)



wherein R^{15} is hydrogen, C_1-C_4 linear alkyl, C_3 or C_4 branched alkyl, trifluoromethyl, $-C(=O)-R^{17}$ or $-C(=O)-O-R^{17}$ wherein R^{17} is C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, C_3-C_{12} cycloalkyl, C_7-C_{12} aralkyl, phenyl or substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above), and the two R^{15}s may be the same or different; R^{16} is hydrogen, C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, phenyl or substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above), or

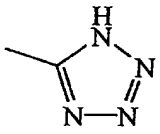
$-C(=O)-R^{18}$ wherein R^{18} represents C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, C_3-C_{12} cycloalkyl, C_7-C_{12} aralkyl, phenyl or substituted phenyl (wherein the substituent

is the same as the substituent defined for the substituted phenyl mentioned above),

(iv) $-CH_2-R^{19}$

wherein R^{19} is

(1)



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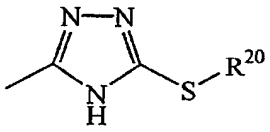
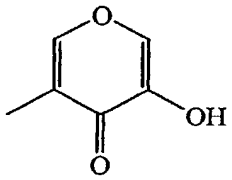


wherein R^{20} is hydrogen, C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, phenyl, substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above), or $-C(=O)-R^{21}$ wherein R^{21} is C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, C_3-C_{12} cycloalkyl, C_7-C_{12} aralkyl, phenyl, or substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above),

(3)



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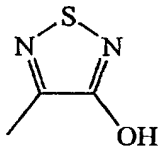

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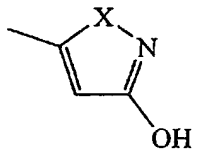


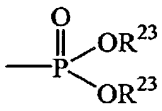
wherein X represents -O- or -S-, or

(6) azide,

(v) $-C(R^{22})_3$

wherein R^{22} represents hydrogen, fluorine, chlorine, bromine, iodine, cyano or C_1-C_4 alkyl, and all of the R^{22}s may be the same or different,

(vi)



wherein R^{23} represents hydrogen, C_1-C_4 alkyl, phenyl, substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above), $-CH_2-OR^{24}$ (wherein R^{24} is C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, C_3-C_{12} cycloalkyl, C_7-C_{12} aralkyl, phenyl, or substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above), or pharmacologically acceptable cation, and the two R^{23}s may be the same or different,

(vii) $-N(R^{25})_2$

wherein R^{25} is hydrogen, C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, C_3-C_{12} cycloalkyl, C_4-C_{13} cycloalkylalkyl, C_7-C_{12} aralkyl, $-C(=O)-R^{26}$,$-C(=O)-O-R^{26}$, $-SO_2-R^{26}$, phenyl or substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above), R^{26} is C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, C_3-C_{12} cycloalkyl, C_7-C_{12} aralkyl, phenyl or substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above), the two R^{25}s may be the same or different (when one of the R^{25}s is

$-SO_2-R^{26}$, the other R^{25} is not $-SO_2-R^{26}$),

(viii) $-(C(=O)CH_2)_k-H$

wherein k represents an integer of 1 or 2, or

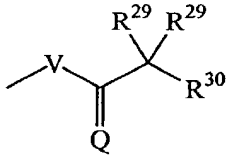
(ix) $-C(=O)-N(R^{27})_2$

wherein R^{27} is hydrogen, C_1-C_{12} alkyl, C_3-C_{12} cycloalkyl, phenyl, substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above), C_4-C_{13} cycloalkylalkyl, C_7-C_{12} aralkyl, cyano or $-SO_2-R^{28}$ wherein R^{28} is C_1-C_{12} alkyl, C_3-C_{12} cycloalkyl, phenyl, substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above), C_4-C_{13} cycloalkylalkyl, or C_7-C_{12} aralkyl, and the two R^{27}s may be the same or different (when one of the R^{27}s is $-SO_2-R^{28}$, the other R^{27} is not $-SO_2-R^{28}$);

Y is hydrogen, C_1-C_4 alkyl, fluorine, chlorine, bromine, formyl, methoxy or nitro;

B is

(i)



wherein V is

(1) $-CH_2CH_2-$,

(2) $-C\equiv C-$,

or

(3) $-CH=C(R^{31})-$

wherein R^{31} is hydrogen, C_1-C_5 alkyl, fluorine, chlorine, bromine or iodine,

Q is

(1) =O

(2)

—R^{32}
—OR^{33}

or

(3)

—R^{32}
—R^{32}

wherein R^{32} is hydrogen, C_1-C_4 linear alkyl, C_3 or C_4 branched alkyl, trifluoromethyl, -C(=O)-R^{34}, or -C(=O)-O-R^{34} wherein R^{34} represents C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, C_3-C_{12} cycloalkyl, C_7-C_{12} aralkyl, phenyl or substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above); R^{33} is hydrogen, C_1-C_4 alkyl, C_1-C_{12} acyl, C_7-C_{16} aroyl, C_7-C_{16} aralkyl, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl, allyl, tert-butyl or tert-butyldimethylsilyl, and the two R^{32}s may be the same or different; R^{29} is hydrogen, fluorine, chlorine, bromine, iodine, cyano or C_1-C_4 alkyl, and the two R^{29}s may be the same or different;

R^{30} is

(1) -Z-R^{35}

wherein Z is defined as the same as the above, R^{35} is C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, C_3-C_{12} cycloalkyl, C_4-C_{13} cycloalkylalkyl, C_3-C_{12} cycloalkyl substituted with 1 to 4 R^{36}s (wherein R^{36} is hydrogen or C_1-C_5 alkyl), C_4-C_{13} cycloalkylalkyl substituted with 1 to 3 R^{36}s (wherein R^{36} is defined as the same as the above), phenyl, substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above), α-naphthyl, β-naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, α-furyl, β-furyl, α-thienyl or β-thienyl,

(2) -Z-O-R^{35}

wherein Z and R^{35} are defined as the same as the above,

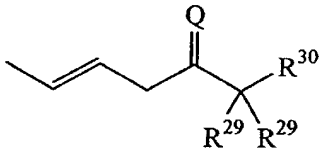
(3) -Z-CH=C(R^{35})$_2$

wherein Z and R^{35} are defined as the same as the above, and the two R^{35}s may be the same or different, or

(4) $-Z-C\equiv C-R^{35}$

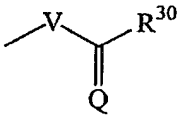
wherein Z and R^{35} are defined as the same as the above,

(ii)



wherein Q, R^{29} and R^{30} are defined as the same as the above, and the two R^{29}s may be the same or different, or

(iii)

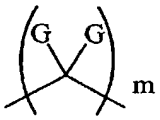


wherein V, Q and R^{30} are defined as the same as the above;

E represents hydrogen or $-OR^{33}$ wherein R^{33} is defined as the same as the above;

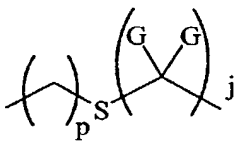
A is

(i)



wherein m represents an integer of 0 to 5, G represents hydrogen, fluorine, chlorine, bromine, iodine, trifuluoromethyl, C_1-C_4 linear alkyl or C_3-C_6 branched alkyl, and all Gs may be the same or different,

(ii)



wherein j represents an integer of 1 to 4, p represents an integer of 0 or 1, G is

defined as the same as the above, and all Gs may be the same or different,

(iii) $-CH=CH-CH_2-$,

(iv) $-CH_2-CH=CH-$,

(v) $-CH_2-O-CH_2-$,

(vi) $-O-CH_2-$,

(vii) $-C\equiv C-$, or

(viii) -C=C- (trans)].

Examples about the above-described Formula (I) will now be described. However, the present invention is not restricted thereto.

Examples of R^2 include hydrogen, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, acetyl, propionyl, benzoyl, phenylacetyl, methoxycarbonyl and ethoxycarbonyl. Among these, preferred are hydrogen, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, tert-butyl and trifluoromethyl, more preferred are hydrogen, methyl, ethyl, propyl, butyl and trifluoromethyl, and still more preferred are hydrogen and methyl.

Examples of R^3 include hydrogen, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, tert-butyl, formyl, acetyl, propionyl, butyloyl, benzoyl, phenylacetyl, 3-phenylpropionyl, 10-phenyldecanoyl, p-phenylbenzoyl, α-naphthoyl, β-naphthoyl, benzyl, phenetyl, 3-phenylpropyl, 6-phenylhexyl, 10-phenyldecyl, p-methylbenzyl, p-ethylbenzyl, p-propylbenzyl, p-pentylbenzyl, p-nonylbenzyl, 3,5-dimethylbenzyl, 3,5-diethylbenzyl, 3,5-dibutylbenzyl, p-phenylbenzyl, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl, allyl, tert-butyl and tert-butyldimethylsilyl. Among these, preferred are hydrogen, acetyl, propionyl, butyloyl, benzoyl, phenylacetyl, 3-phenylpropionyl, 10-phenyldecanoyl, p-phenylbenzoyl, α-naphthoyl, β-naphthoyl, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl, allyl and tert-butyldimethylsilyl, more preferred are hydrogen, acetyl, tetrahydropyranyl, tetrahydrofuranyl and tert-butyldimethylsilyl, and still more preferred is hydrogen.

Examples of R^4 include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, dodecyl, isopropyl, isobutyl, tert-butyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1-methylheptyl, 2-methylheptyl, 3-methylheptyl, 4-methylheptyl, 5-methylheptyl, 6-methylheptyl, 1-methyloctyl, 2-methyloctyl, 3-methyloctyl, 4-methyloctyl, 5-methyloctyl, 6-methyloctyl, 7-methyloctyl, 1-methylnonyl, 2-methylnonyl, 1-methyldecanyl, 2-methyldecanyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,1-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,1-dimethylhexyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 5,5-dimethylhexyl, 1,1-dimethylheptyl, 2,2-dimethylheptyl, 3,3-dimethylheptyl, 4,4-dimethylheptyl, 5,5-dimethylheptyl, 6,6-dimethylheptyl, 1,1-dimethyloctyl, 2,2-dimethyloctyl, 3,3-dimethyloctyl, 1,1-dimethylnonyl, 2,2-dimethylnonyl, 3,3-dimethylnonyl, 1,1-dimethyldecanyl, 2,2-dimethyldecanyl, 3,3-dimethyldecanyl, 1,1,2,2-tetramethylpentyl, 1,1,3,3-tetramethylpentyl, 1,1,2,2-tetramethylhexyl, 1,1,3,3-tetramethylhexyl, 2,2,3,3-tetramethylhexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclododecyl, benzyl, phenetyl, 3-phenylpropyl, 6-phenylhexyl, p-methylbenzyl, p-ethylbenzyl, p-propylbenzyl, p-pentylbenzyl, 3,5-dimethylbenzyl, 3,5-diethylbenzyl, phenyl, p-fluorophenyl, p-nitrophenyl and p-methoxyphenyl. Among these, preferred are methyl, ethyl, propyl, butyl and phenyl, more preferred are methyl, ethyl and phenyl, and still more preferred are methyl and phenyl.

Preferred examples of R^5 include hydrogen, lithium ion, sodium ion, potassium ion, magnesium ion, calcium ion, cations derived from amines (e.g., methylamine, dimethylamine, triethylamine, ethylamine, dibutylamine, triisopropylamine, N-methylhexylamine, decylamine, dodecylamine, allylamine, crotylamine, cyclopentylamine, dicyclohexylamine, benzylamine, dibenzylamine, α-

phenylethylamine, β-phenylethylamine, ethylenediamine, diethylenetriamine, 1-methylpiperidine, 4-ethylmorpholine, 1-isopropylpyrrolidine, 2-methylpyrrolidine, 1,4-dimethylpiperazine, 2-methylpiperidine, mono-, di-, and triethanolamine, ethyldiethanolamine, N-butylethanolamine, 2-amino-1-butanol, 2-amino-2-ethyl-1,3-propanediol, tris(hydroxymethyl)aminomethane, N-phenylethanolamine, N-(p-tert-aminophenyl)diethanolamine, galactamine, N-methylglutamine, N-methylglucosamine, ephedrine, phenylephrine, epinephrine, procaine, lysine and arginine), methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and dodecyl. Among these, more preferred are hydrogen, lithium ion, sodium ion, potassium ion, magnesium ion, calcium ion, cations derived from amines (triethylamine, ethylenediamine, diethylenetriamine, and mono-, di- and triethanolamine), methyl, ethyl, propyl and butyl, and still more preferred are hydrogen, sodium ion and methyl.

Examples of R^6 include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclododecyl, 2-methylcyclopropyl, 3-methylcyclobutyl, 3-methylcyclopentyl, 4-methylcyclohexyl, 4-methylcycloheptyl, 5-methylcyclooctyl and 5-methylcyclononyl. Among these, preferred are cyclopentyl, cyclohexyl, cycloheptyl, 3-methylcyclopentyl, 4-methylcyclohexyl and 4-methylcycloheptyl, and more preferred are cyclohexyl and 4-methylcyclohexyl, still more preferred is cyclohexyl.

Examples of R^7 include hydrogen, methyl, ethyl, propyl, butyl, isopropyl, isobutyl and tert-butyl. Among these, preferred are hydrogen, methyl, ethyl, isopropyl and tert-butyl, still more preferred are hydrogen, methyl and ethyl, and still more preferred are hydrogen and methyl.

Examples of R^8 include hydrogen, methyl, ethyl, propyl, butyl, isopropyl, isobutyl and tert-butyl. Among these, preferred are hydrogen, methyl, ethyl, isopropyl and tert-butyl, still more preferred are hydrogen, methyl and ethyl, and still more preferred are hydrogen and methyl.

Examples of R^9 include hydrogen, methyl, ethyl, propyl, butyl, isopropyl, isobutyl and tert-butyl. Among these, preferred are hydrogen, methyl, ethyl, isopropyl and tert-butyl, still more preferred are hydrogen, methyl and ethyl, and still more preferred are hydrogen and methyl.

R^{10} represents hydrogen or benzoyl, and hydrogen is especially preferred.

R^{11} represents phenyl, p-bromophenyl, p-chlorophenyl, p-biphenyl, p-nitrophenyl, p-benzamidephenyl or 2-naphthyl, preferably phenyl, p-bromophenyl, p-chlorophenyl, p-biphenyl or p-nitrophenyl, more preferably phenyl, p-chlorophenyl or p-biphenyl, still more preferably phenyl.

Examples of R^{12} include hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, dodecyl, isopropyl, isobutyl, tert-butyl, 4-methylpentyl, 5-methylhexyl, 6-methylheptyl, 7-methyloctyl, benzyl, phenetyl, 3-phenylpropyl, 6-phenylhexyl, p-methylbenzyl, p-ethylbenzyl, p-propylbenzyl, p-pentylbenzyl, 3,5-dimethylbenzyl and 3,5-diethylbenzyl. Among these, preferred are hydrogen, methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, benzyl, phenetyl and 3-phenylpropyl, more preferred are hydrogen, methyl, ethyl, isopropyl, isobutyl, benzyl and phenetyl, and still more preferred are hydrogen, methyl, isopropyl and benzyl.

Examples of R^{13} include hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, dodecyl, isopropyl, isobutyl, tert-butyl, 4-methylpentyl, 5-methylhexyl, 6-methylheptyl, 7-methyloctyl, benzyl, phenetyl, 3-phenylpropyl, 6-phenylhexyl, p-methylbenzyl, p-ethylbenzyl, p-propylbenzyl, p-pentylbenzyl, 3,5-dimethylbenzyl and 3,5-diethylbenzyl. Among these, preferred are hydrogen, methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, benzyl, phenetyl and 3-phenylpropyl, more preferred are hydrogen, methyl, ethyl, isopropyl, isobutyl, benzyl and phenetyl, and still more preferred are hydrogen, methyl, isopropyl and benzyl.

Examples of R^{14} include methyl, ethyl, propyl, butyl, pentyl, hexyl, octyl, hexadecanyl, octaeicosanyl, acetyl, octanoyl, decanoyl, palmitoyl, eicosanoyl and

hexaeicosanoyl. Among these, preferred are methyl, ethyl, propyl, acetyl, octanoyl and decanoyl, more preferred are methyl, ethyl, acetyl and octanoyl, and still more preferred are methyl and acetyl.

Examples of R^{15} include hydrogen, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, acetyl, propionyl, benzoyl, phenylacetyl, methoxycarbonyl and ethoxycarbonyl. Among these, preferred are hydrogen, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, tert-butyl and trifluoromethyl, more preferred are hydrogen, methyl, ethyl, propyl, butyl and trifluoromethyl, and still more preferred are hydrogen and methyl.

Examples of R^{16} include hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, dodecyl, isopropyl, isobutyl, tert-butyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1-methylheptyl, 2-methylheptyl, 3-methylheptyl, 4-methylheptyl, 5-methylheptyl, 6-methylheptyl, 1-methyloctyl, 2-methyloctyl, 3-methyloctyl, 4-methyloctyl, 5-methyloctyl, 6-methyloctyl, 7-methyloctyl, 1-methylnonyl, 2-methylnonyl, 1-methyldecanyl, 2-methyldecanyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,1-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,1-dimethylhexyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 5,5-dimethylhexyl, 1,1-dimethylheptyl, 2,2-dimethylheptyl, 3,3-dimethylheptyl, 4,4-dimethylheptyl, 5,5-dimethylheptyl, 6,6-dimethylheptyl, 1,1-dimethyloctyl, 2,2-dimethyloctyl, 3,3-dimethyloctyl, 1,1-dimethylnonyl, 2,2-dimethylnonyl, 3,3-dimethylnonyl, 1,1-dimethyldecanyl, 2,2-dimethyldecanyl, 3,3-dimethyldecanyl, 1,1,2,2-tetramethylpentyl, 1,1,3,3-tetramethylpentyl, 1,1,2,2-tetramethylhexyl, 1,1,3,3-tetramethylhexyl, 2,2,3,3-tetramethylhexyl, phenyl, p-fluorophenyl, p-nitrophenyl, p-methoxyphenyl, acetyl and propionyl. Among these, preferred are hydrogen, methyl, ethyl, propyl, butyl, phenyl, acetyl and propionyl,

more preferred are hydrogen, methyl, ethyl, propyl, phenyl and acetyl, and still more preferred are hydrogen, methyl, phenyl and acetyl.

Examples of R^{17} include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, dodecyl, isopropyl, isobutyl, tert-butyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1-methylheptyl, 2-methylheptyl, 3-methylheptyl, 4-methylheptyl, 5-methylheptyl, 6-methylheptyl, 1-methyloctyl, 2-methyloctyl, 3-methyloctyl, 4-methyloctyl, 5-methyloctyl, 6-methyloctyl, 7-methyloctyl, 1-methylnonyl, 2-methylnonyl, 1-methyldecanyl, 2-methyldecanyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,1-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,1-dimethylhexyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 5,5-dimethylhexyl, 1,1-dimethylheptyl, 2,2-dimethylheptyl, 3,3-dimethylheptyl, 4,4-dimethylheptyl, 5,5-dimethylheptyl, 6,6-dimethylheptyl, 1,1-dimethyloctyl, 2,2-dimethyloctyl, 3,3-dimethyloctyl, 1,1-dimethylnonyl, 2,2-dimethylnonyl, 3,3-dimethylnonyl, 1,1-dimethyldecanyl, 2,2-dimethyldecanyl, 3,3-dimethyldecanyl, 1,1,2,2-tetramethylpentyl, 1,1,3,3-tetramethylpentyl, 1,1,2,2-tetramethylhexyl, 1,1,3,3-tetramethylhexyl, 2,2,3,3-tetramethylhexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclododecyl, benzyl, phenetyl, 3-phenylpropyl, 6-phenylhexyl, p-methylbenzyl, p-ethylbenzyl, p-propylbenzyl, p-pentylbenzyl, 3,5-dimethylbenzyl, 3,5-diethylbenzyl, phenyl, p-fluorophenyl, p-nitrophenyl and p-methoxyphenyl. Among these, preferred are methyl, ethyl, propyl, butyl and phenyl, more preferred are methyl, ethyl and phenyl, and still more preferred are methyl and phenyl.

Examples of R^{18} include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, dodecyl, isopropyl, isobutyl, tert-butyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-

methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1-methylheptyl, 2-methylheptyl, 3-methylheptyl, 4-methylheptyl, 5-methylheptyl, 6-methylheptyl, 1-methyloctyl, 2-methyloctyl, 3-methyloctyl, 4-methyloctyl, 5-methyloctyl, 6-methyloctyl, 7-methyloctyl, 1-methylnonyl, 2-methylnonyl, 1-methyldecanyl, 2-methyldecanyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,1-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,1-dimethylhexyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 5,5-dimethylhexyl, 1,1-dimethylheptyl, 2,2-dimethylheptyl, 3,3-dimethylheptyl, 4,4-dimethylheptyl, 5,5-dimethylheptyl, 6,6-dimethylheptyl, 1,1-dimethyloctyl, 2,2-dimethyloctyl, 3,3-dimethyloctyl, 1,1-dimethylnonyl, 2,2-dimethylnonyl, 3,3-dimethylnonyl, 1,1-dimethyldecanyl, 2,2-dimethyldecanyl, 3,3-dimethyldecanyl, 1,1,2,2-tetramethylpentyl, 1,1,3,3-tetramethylpentyl, 1,1,2,2-tetramethylhexyl, 1,1,3,3-tetramethylhexyl, 2,2,3,3-tetramethylhexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclododecyl, benzyl, phenetyl, 3-phenylpropyl, 6-phenylhexyl, p-methylbenzyl, p-ethylbenzyl, p-propylbenzyl, p-pentylbenzyl, 3,5-dimethylbenzyl, 3,5-diethylbenzyl, phenyl, p-fluorophenyl, p-nitrophenyl and p-methoxyphenyl. Among these, preferred are methyl, ethyl, propyl, butyl and phenyl, more preferred are methyl, ethyl and phenyl, and still more preferred are methyl and phenyl.

Examples of R^{20} include hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, dodecyl, isopropyl, isobutyl, tert-butyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1-methylheptyl, 2-methylheptyl, 3-methylheptyl, 4-methylheptyl, 5-methylheptyl, 6-methylheptyl, 1-methyloctyl, 2-methyloctyl, 3-methyloctyl, 4-methyloctyl, 5-methyloctyl, 6-methyloctyl, 7-methyloctyl, 1-methylnonyl, 2-methylnonyl, 1-methyldecanyl, 2-methyldecanyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-

dimethylbutyl, 1,1-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,1-dimethylhexyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 5,5-dimethylhexyl, 1,1-dimethylheptyl, 2,2-dimethylheptyl, 3,3-dimethylheptyl, 4,4-dimethylheptyl, 5,5-dimethylheptyl, 6,6-dimethylheptyl, 1,1-dimethyloctyl, 2,2-dimethyloctyl, 3,3-dimethyloctyl, 1,1-dimethylnonyl, 2,2-dimethylnonyl, 3,3-dimethylnonyl, 1,1-dimethyldecanyl, 2,2-dimethyldecanyl, 3,3-dimethyldecanyl, 1,1,2,2-tetramethylpentyl, 1,1,3,3-tetramethylpentyl, 1,1,2,2-tetramethylhexyl, 1,1,3,3-tetramethylhexyl, 2,2,3,3-tetramethylhexyl, phenyl, p-fluorophenyl, p-nitrophenyl, p-methoxyphenyl, acetyl and propionyl. Among these, preferred are hydrogen, methyl, ethyl, propyl, butyl, phenyl, acetyl and propionyl, more preferred are hydrogen, methyl, ethyl, propyl, phenyl and acetyl, and still more preferred are hydrogen, methyl, phenyl and acetyl.

Examples of R^{21} include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, dodecyl, isopropyl, isobutyl, tert-butyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1-methylheptyl, 2-methylheptyl, 3-methylheptyl, 4-methylheptyl, 5-methylheptyl, 6-methylheptyl, 1-methyloctyl, 2-methyloctyl, 3-methyloctyl, 4-methyloctyl, 5-methyloctyl, 6-methyloctyl, 7-methyloctyl, 1-methylnonyl, 2-methylnonyl, 1-methyldecanyl, 2-methyldecanyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,1-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,1-dimethylhexyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 5,5-dimethylhexyl, 1,1-dimethylheptyl, 2,2-dimethylheptyl, 3,3-dimethylheptyl, 4,4-dimethylheptyl, 5,5-dimethylheptyl, 6,6-dimethylheptyl, 1,1-dimethyloctyl, 2,2-dimethyloctyl, 3,3-dimethyloctyl, 1,1-dimethylnonyl, 2,2-dimethylnonyl, 3,3-dimethylnonyl, 1,1-dimethyldecanyl, 2,2-dimethyldecanyl, 3,3-dimethyldecanyl, 1,1,2,2-tetramethylpentyl, 1,1,3,3-tetramethylpentyl, 1,1,2,2-

tetramethylhexyl, 1,1,3,3-tetramethylhexyl, 2,2,3,3-tetramethylhexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclododecyl, benzyl, phenetyl, 3-phenylpropyl, 6-phenylhexyl, p-methylbenzyl, p-ethylbenzyl, p-propylbenzyl, p-pentylbenzyl, 3,5-dimethylbenzyl, 3,5-diethylbenzyl, phenyl, p-fluorophenyl, p-nitrophenyl and p-methoxyphenyl. Among these, preferred are methyl, ethyl, propyl, butyl and phenyl, more preferred are methyl, ethyl and phenyl, and still more preferred are methyl and phenyl.

Examples of R^{22} include hydrogen, fluorine, chlorine, bromine, iodine, cyano, methyl, ethyl, propyl, butyl, isopropyl, isobutyl and tert-butyl. Among these, preferred are hydrogen, fluorine, cyano, methyl, ethyl, propyl, butyl, isopropyl, isobutyl and tert-butyl, more preferred are hydrogen, fluorine, methyl, ethyl and isopropyl, and still more preferred are hydrogen, fluorine and methyl.

Examples of R^{23} include hydrogen, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, tert-butyl, phenyl, p-fluorophenyl, p-nitrophenyl, p-methoxyphenyl, methoxymethyl, ethoxymethyl, lithium ion, sodium ion, potassium ion, magnesium ion, calcium ion, and cations derived from amines (e.g., methylamine, dimethylamine, triethylamine, ethylamine, dibutylamine, triisopropylamine, N-methylhexylamine, decylamine, dodecylamine, allylamine, crotylamine, cyclopentylamine, dicyclohexylamine, benzylamine, dibenzylamine, α-phenylethylamine, β-phenylethylamine, ethylenediamine, diethylenetriamine, 1-methylpiperidine, 4-ethylmorpholine, 1-isopropylpyrrolidine, 2-methylpyrrolidine, 1,4-dimethylpiperazine, 2-methylpiperidine, mono-, di-, and triethanolamine, ethyldiethanolamine, N-butylethanolamine, 2-amino-1-butanol, 2-amino-2-ethyl-1,3-propanediol, tris(hydroxymethyl)aminomethane, N-phenylethanolamine, N-(p-tert-amylphenyl)diethanolamine, galactamine, N-methylglutamine, N-methylglucosamine, ephedrine, phenylephrine, epinephrine, procaine, lysine and arginine). Among these, preferred are hydrogen, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, tert-butyl,

lithium ion, sodium ion, potassium ion, magnesium ion, calcium ion, and cations derived from amines (triethylamine, ethylenediamine, diethylenetriamine, and mono-, di-, and triethanolamine), more preferred are hydrogen, methyl, isopropyl, lithium ion, sodium ion, potassium ion, magnesium ion and calcium ion, and still more preferred are hydrogen, methyl and sodium ion.

Examples of R^{24} include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, dodecyl, isopropyl, isobutyl, tert-butyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1-methylheptyl, 2-methylheptyl, 3-methylheptyl, 4-methylheptyl, 5-methylheptyl, 6-methylheptyl, 1-methyloctyl, 2-methyloctyl, 3-methyloctyl, 4-methyloctyl, 5-methyloctyl, 6-methyloctyl, 7-methyloctyl, 1-methylnonyl, 2-methylnonyl, 1-methyldecanyl, 2-methyldecanyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,1-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,1-dimethylhexyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 5,5-dimethylhexyl, 1,1-dimethylheptyl, 2,2-dimethylheptyl, 3,3-dimethylheptyl, 4,4-dimethylheptyl, 5,5-dimethylheptyl, 6,6-dimethylheptyl, 1,1-dimethyloctyl, 2,2-dimethyloctyl, 3,3-dimethyloctyl, 1,1-dimethylnonyl, 2,2-dimethylnonyl, 3,3-dimethylnonyl, 1,1-dimethyldecanyl, 2,2-dimethyldecanyl, 3,3-dimethyldecanyl, 1,1,2,2-tetramethylpentyl, 1,1,3,3-tetramethylpentyl, 1,1,2,2-tetramethylhexyl, 1,1,3,3-tetramethylhexyl, 2,2,3,3-tetramethylhexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclododecyl, benzyl, phenetyl, 3-phenylpropyl, 6-phenylhexyl, p-methylbenzyl, p-ethylbenzyl, p-propylbenzyl, p-pentylbenzyl, 3,5-dimethylbenzyl, 3,5-diethylbenzyl, phenyl, p-fluorophenyl, p-nitrophenyl and p-methoxyphenyl. Among these, preferred are methyl, ethyl, propyl, butyl and phenyl, more preferred are methyl, ethyl and phenyl, and still more preferred are methyl and phenyl.

Examples of R^{25} include hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, dodecyl, isopropyl, isobutyl, tert-butyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1-methylheptyl, 2-methylheptyl, 3-methylheptyl, 4-methylheptyl, 5-methylheptyl, 6-methylheptyl, 1-methyloctyl, 2-methyloctyl, 3-methyloctyl, 4-methyloctyl, 5-methyloctyl, 6-methyloctyl, 7-methyloctyl, 1-methylnonyl, 2-methylnonyl, 1-methyldecanyl, 2-methyldecanyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,1-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,1-dimethylhexyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 5,5-dimethylhexyl, 1,1-dimethylheptyl, 2,2-dimethylheptyl, 3,3-dimethylheptyl, 4,4-dimethylheptyl, 5,5-dimethylheptyl, 6,6-dimethylheptyl, 1,1-dimethyloctyl, 2,2-dimethyloctyl, 3,3-dimethyloctyl, 1,1-dimethylnonyl, 2,2-dimethylnonyl, 3,3-dimethylnonyl, 1,1-dimethyldecanyl, 2,2-dimethyldecanyl, 3,3-dimethyldecanyl, 1,1,2,2-tetramethylpentyl, 1,1,3,3-tetramethylpentyl, 1,1,2,2-tetramethylhexyl, 1,1,3,3-tetramethylhexyl, 2,2,3,3-tetramethylhexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclododecyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, cyclododecylmethyl, 2-cyclopropylethyl, 2-cyclobutylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, 2-cycloheptylethyl, 3-cyclopropylpropyl, 3-cyclobutylpropyl, 3-cyclopentylpropyl, 3-cyclopentylpropyl, 3-cyclohexylpropyl, 3-cycloheptylpropyl, 6-cyclopropylhexyl, 6-cyclobutylhexyl, 6-cyclopentylhexyl, 6-cyclohexylhexyl, 6-cycloheptylhexyl, benzyl, phenetyl, 3-phenylpropyl, 6-phenylhexyl, p-methylbenzyl, p-ethylbenzyl, p-propylbenzyl, p-pentylbenzyl, 3,5-dimethylbenzyl, 3,5-diethylbenzyl, acetyl, propionyl, benzoyl, phenylacetyl, methoxycarbonyl, ethoxycarbonyl, methylsulfonyl, ethylsulfonyl, phenylsulfonyl, phenyl, p-fluorophenyl, p-nitrophenyl and p-methoxyphenyl.

Among these, preferred are hydrogen, p-methylbenzyl, p-ethylbenzyl, p-propylbenzyl, p-pentylbenzyl, 3,5-dimethylbenzyl, 3,5-diethylbenzyl, acetyl, propionyl, benzoyl, pyhenylacetyl, methoxycarbonyl, ethoxycarbonyl, methylsulfonyl, ethylsulfonyl, phenylsulfonyl, phenyl, p-fluorophenyl, p-nitrophenyl and p-methoxyphenyl, more preferred are hydrogen, acetyl, propionyl, benzoyl, phenylacetyl, methylsulfonyl, ethylsulfonyl and phenylsulfonyl, and still more preferred are hydrogen, acetyl, benzoyl, methylsulfonyl and phenylsulfonyl.

Examples of R^{26} include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, dodecyl, isopropyl, isobutyl, tert-butyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1-methylheptyl, 2-methylheptyl, 3-methylheptyl, 4-methylheptyl, 5-methylheptyl, 6-methylheptyl, 1-methyloctyl, 2-methyloctyl, 3-methyloctyl, 4-methyloctyl, 5-methyloctyl, 6-methyloctyl, 7-methyloctyl, 1-methylnonyl, 2-methylnonyl, 1-methyldecanyl, 2-methyldecanyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,1-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,1-dimethylhexyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 5,5-dimethylhexyl, 1,1-dimethylheptyl, 2,2-dimethylheptyl, 3,3-dimethylheptyl, 4,4-dimethylheptyl, 5,5-dimethylheptyl, 6,6-dimethylheptyl, 1,1-dimethyloctyl, 2,2-dimethyloctyl, 3,3-dimethyloctyl, 1,1-dimethylnonyl, 2,2-dimethylnonyl, 3,3-dimethylnonyl, 1,1-dimethyldecanyl, 2,2-dimethyldecanyl, 3,3-dimethyldecanyl, 1,1,2,2-tetramethylpentyl, 1,1,3,3-tetramethylpentyl, 1,1,2,2-tetramethylhexyl, 1,1,3,3-tetramethylhexyl, 2,2,3,3-tetramethylhexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclododecyl, benzyl, phenetyl, 3-phenylpropyl, 6-phenylhexyl, p-methylbenzyl, p-ethylbenzyl, p-propylbenzyl, p-pentylbenzyl, 3,5-dimethylbenzyl, 3,5-diethylbenzyl, phenyl, p-fluorophenyl, p-nitrophenyl and p-methoxyphenyl. Among these,

preferred are methyl, ethyl, propyl, butyl and phenyl, more preferred are methyl, ethyl and phenyl, and still more preferred are methyl and phenyl.

Examples of R^{27} include hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, dodecyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclododecyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, cyclododecylmethyl, 2-cyclopropylethyl, 2-cyclobutylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, 2-cycloheptylethyl, 3-cyclopropylpropyl, 3-cyclobutylpropyl, 3-cyclopentylpropyl, 3-cyclopentylpropyl, 3-cyclohexylpropyl, 3-cycloheptylpropyl, 6-cyclopropylhexyl, 6-cyclobutylhexyl, 6-cyclopentylhexyl, 6-cyclohexylhexyl, 6-cycloheptylhexyl, benzyl, phenetyl, 3-phenylpropyl, 6-phenylhexyl, p-methylbenzyl, p-ethylbenzyl, p-propylbenzyl, p-pentylbenzyl, 3,5-dimethylbenzyl, 3,5-diethylbenzyl, cyano, methylsulfonyl, ethylsulfonyl, phenylsulfonyl, phenyl, p-fluorophenyl, p-nitrophenyl and p-methoxyphenyl. Among these, preferred are hydrogen, p-methylbenzyl, p-ethylbenzyl, p-propylbenzyl, p-pentylbenzyl, 3,5-dimethylbenzyl, 3,5-diethylbenzyl, cyano, methylsulfonyl, ethylsulfonyl, phenylsulfonyl, phenyl, p-fluorophenyl, p-nitrophenyl and p-methoxyphenyl, more preferred are hydrogen, cyano, methylsulfonyl, ethylsulfonyl and phenylsulfonyl, and still more preferred are hydrogen, cyano, methylsulfonyl and phenylsulfonyl.

Examples of R^{28} include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, dodecyl, isopropyl, isobutyl, tert-butyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1-methylheptyl, 2-methylheptyl, 3-methylheptyl, 4-methylheptyl, 5-methylheptyl, 6-methylheptyl, 1-methyloctyl, 2-methyloctyl, 3-methyloctyl, 4-methyloctyl, 5-methyloctyl, 6-methyloctyl, 7-methyloctyl, 1-methylnonyl, 2-methylnonyl, 1-methyldecanyl, 2-methyldecanyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-

dimethylbutyl, 1,1-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,1-dimethylhexyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 5,5-dimethylhexyl, 1,1-dimethylheptyl, 2,2-dimethylheptyl, 3,3-dimethylheptyl, 4,4-dimethylheptyl, 5,5-dimethylheptyl, 6,6-dimethylheptyl, 1,1-dimethyloctyl, 2,2-dimethyloctyl, 3,3-dimethyloctyl, 1,1-dimethylnonyl, 2,2-dimethylnonyl, 3,3-dimethylnonyl, 1,1-dimethyldecanyl, 2,2-dimethyldecanyl, 3,3-dimethyldecanyl, 1,1,2,2-tetramethylpentyl, 1,1,3,3-tetramethylpentyl, 1,1,2,2-tetramethylhexyl, 1,1,3,3-tetramethylhexyl, 2,2,3,3-tetramethylhexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclododecyl, benzyl, phenetyl, 3-phenylpropyl, 6-phenylhexyl, p-methylbenzyl, p-ethylbenzyl, p-propylbenzyl, p-pentylbenzyl, 3,5-dimethylbenzyl, 3,5-diethylbenzyl, phenyl, p-fluorophenyl, p-nitrophenyl and p-methoxyphenyl. Among these, preferred are methyl, ethyl, propyl, butyl and phenyl, more preferred are methyl, ethyl and phenyl, and still more preferred are methyl and phenyl.

Examples of R^{29} include hydrogen, fluorine, chlorine, bromine, iodine, cyano, methyl, ethyl, propyl, butyl, isopropyl, isobutyl and tert-butyl. Among these, preferred are hydrogen, fluorine, cyano, methyl, ethyl, propyl, butyl, isopropyl, isobutyl and tert-butyl, more preferred are hydrogen, fluorine, methyl, ethyl and isopropyl, and still more preferred are hydrogen, fluorine and methyl.

Examples of R^{31} include hydrogen, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, tert-butyl, fluorine, chlorine, bromine and iodine. Among these, preferred are hydrogen, methyl, ethyl, isopropyl, tert-butyl and fluorine, more preferred are hydrogen, methyl and ethyl, and still more preferred are hydrogen and methyl.

Examples of R^{32} include hydrogen, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, acetyl, propionyl, benzoyl, phenylacetyl, methoxycarbonyl and ethoxycarbonyl. Among these, preferred are hydrogen, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, tert-butyl and trifluoromethyl, more

preferred are hydrogen, methyl, ethyl, propyl, butyl and trifluoromethyl, and still more preferred are hydrogen and methyl.

Examples of R^{33} include hydrogen, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, tert-butyl, formyl, acetyl, propionyl, butyloyl, benzoyl, phenylacetyl, 3-phenylpropionyl, 10-phenyldecanoyl, p-phenylbenzoyl, α-naphthoyl, β-naphthoyl, benzyl, phenetyl, 3-phenylpropyl, 6-phenylhexyl, 10-phenyldecyl, p-methylbenzyl, p-ethylbenzyl, p-propylbenzyl, p-pentylbenzyl, p-nonylbenzyl, 3,5-dimethylbenzyl, 3,5-diethylbenzyl, 3,5-dibutylbenzyl, p-phenylbenzyl, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl, allyl, tert-butyl and tert-butyldimethylsilyl. Among these, preferred are hydrogen, acetyl, propionyl, butyloyl, benzoyl, phenylacetyl, 3-phenylpropionyl, 10-phenyldecanoyl, p-phenylbenzoyl, α-naphthoyl, β-naphthoyl, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl, allyl and tert-butyldimethylsilyl, more preferred are hydrogen, acetyl, tetrahydropyranyl, tetrahydrofuranyl and tert-butyldimethylsilyl, and still more preferred is hydrogen.

Examples of R^{34} include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, dodecyl, isopropyl, isobutyl, tert-butyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1-methylheptyl, 2-methylheptyl, 3-methylheptyl, 4-methylheptyl, 5-methylheptyl, 6-methylheptyl, 1-methyloctyl, 2-methyloctyl, 3-methyloctyl, 4-methyloctyl, 5-methyloctyl, 6-methyloctyl, 7-methyloctyl, 1-methylnonyl, 2-methylnonyl, 1-methyldecanyl, 2-methyldecanyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,1-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,1-dimethylhexyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 5,5-dimethylhexyl, 1,1-dimethylheptyl, 2,2-dimethylheptyl, 3,3-dimethylheptyl, 4,4-dimethylheptyl, 5,5-dimethylheptyl, 6,6-dimethylheptyl, 1,1-dimethyloctyl, 2,2-dimethyloctyl, 3,3-dimethyloctyl, 1,1-dimethylnonyl, 2,2-

dimethylnonyl, 3,3-dimethylnonyl, 1,1-dimethyldecanyl, 2,2-dimethyldecanyl, 3,3-dimethyldecanyl, 1,1,2,2-tetramethylpentyl, 1,1,3,3-tetramethylpentyl, 1,1,2,2-tetramethylhexyl, 1,1,3,3-tetramethylhexyl, 2,2,3,3-tetramethylhexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclododecyl, benzyl, phenetyl, 3-phenylpropyl, 6-phenylhexyl, p-methylbenzyl, p-ethylbenzyl, p-propylbenzyl, p-pentylbenzyl, 3,5-dimethylbenzyl, 3,5-diethylbenzyl, phenyl, p-fluorophenyl, p-nitrophenyl and p-methoxyphenyl. Among these, preferred are methyl, ethyl, propyl, butyl and phenyl, more preferred are methyl, ethyl and phenyl, and still more preferred are methyl and phenyl.

Examples of R^{35} include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, dodecyl, isopropyl, isobutyl, tert-butyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1-methylheptyl, 2-methylheptyl, 3-methylheptyl, 4-methylheptyl, 5-methylheptyl, 6-methylheptyl, 1-methyloctyl, 2-methyloctyl, 3-methyloctyl, 4-methyloctyl, 5-methyloctyl, 6-methyloctyl, 7-methyloctyl, 1-methylnonyl, 2-methylnonyl, 1-methyldecanyl, 2-methyldecanyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,1-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,1-dimethylhexyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 5,5-dimethylhexyl, 1,1-dimethylheptyl, 2,2-dimethylheptyl, 3,3-dimethylheptyl, 4,4-dimethylheptyl, 5,5-dimethylheptyl, 6,6-dimethylheptyl, 1,1-dimethyloctyl, 2,2-dimethyloctyl, 3,3-dimethyloctyl, 1,1-dimethylnonyl, 2,2-dimethylnonyl, 3,3-dimethylnonyl, 1,1-dimethyldecanyl, 2,2-dimethyldecanyl, 3,3-dimethyldecanyl, 1,1,2,2-tetramethylpentyl, 1,1,3,3-tetramethylpentyl, 1,1,2,2-tetramethylhexyl, 1,1,3,3-tetramethylhexyl, 2,2,3,3-tetramethylhexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclododecyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl,

cyclohexylmethyl, cycloheptylmethyl, cyclododecylmethyl, 2-cyclopropylethyl, 2-cyclobutylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, 2-cycloheptylethyl, 3-cyclopropylpropyl, 3-cyclobutylpropyl, 3-cyclopentylpropyl, 3-cyclopentylpropyl, 3-cyclohexylpropyl, 3-cycloheptylpropyl, 6-cyclopropylhexyl, 6-cyclobutylhexyl, 6-cyclopentylhexyl, 6-cyclohexylhexyl, 6-cycloheptylhexyl, 2-methylcyclopropyl, 3-methylcyclobutyl, 3-methylcyclopentyl, 4-methylcyclohexyl, 4-methylcycloheptyl, 5-methylcyclooctyl, 5-methylcyclononyl, 2-methylcyclopropylmethyl, 3-methylcyclobutylmethyl, 3-methylcyclopentylmethyl, 4-methylcyclohexylmethyl, 4-methylcycloheptylmethyl, 5-methylcyclooctylmethyl, 5-methylcyclononylmethyl, phenyl, p-fluorophenyl, p-nitrophenyl, p-methoxyphenyl, α-naphthyl, β-naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, α-furyl, β-furyl, α-thienyl and β-thienyl. Among these, preferred are methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, isobutyl, tert-butyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1-methylheptyl, 2-methylheptyl, 3-methylheptyl, 4-methylheptyl, 5-methylheptyl, 6-methylheptyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,1-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,1-dimethylhexyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 5,5-dimethylhexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclododecyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-methylcyclopropyl, 3-methylcyclobutyl, 3-methylcyclopentyl, 4-methylcyclohexyl, 4-methylcycloheptyl, 5-methylcyclooctyl, 5-methylcyclononyl, 2-methylcyclopropylmethyl, 3-methylcyclobutylmethyl, 3-methylcyclopentylmethyl, phenyl, p-fluorophenyl, p-nitrophenyl and p-methoxyphenyl, more preferred are methyl, ethyl, propyl, butyl, isopropyl, isobutyl, tert-butyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl,

2,2-dimethylbutyl, 3,3-dimethylbutyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-methylcyclopropyl, 3-methylcyclobutyl, 3-methylcyclopentyl, 4-methylcyclohexyl, 4-methylcycloheptyl, 5-methylcyclooctyl, 2-methylcyclopropylmethyl, 3-methylcyclobutylmethyl, 3-methylcyclopentylmethyl and phenyl, and still more preferred are cyclopentyl, cyclohexyl, cycloheptyl and phenyl.

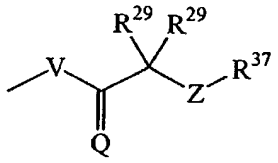
Examples of R^{36} include hydrogen, methyl, ethyl, propyl, butyl, isopropyl, isobutyl and tert-butyl. Among these, preferred are hydrogen, methyl, ethyl, isopropyl and tert-butyl, more preferred are hydrogen, methyl and ethyl, and still more preferred are hydrogen and methyl.

Examples of G include hydrogen, fluorine, chlorine, bromine, iodine, trifluoromethyl, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, tert-butyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl and 3,3-dimethylbutyl. Among these, preferred are hydrogen, fluorine, chlorine, bromine, iodine, trifluoromethyl, methyl, ethyl, propyl and butyl, more preferred are hydrogen, fluorine, methyl, ethyl, propyl and butyl, and still more preferred are hydrogen and fluorine.

Examples of Y include hydrogen, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, tert-butyl, fluorine, chlorine, bromine, formyl, methoxy and nitro. Among these, preferred are hydrogen, methyl, fluorine, chlorine, bromine, and formyl, more preferred are hydrogen, methyl and fluorine, and still more preferred is hydrogen.

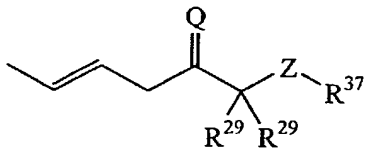
Among the 5,6,7-trinor-4,8-inter-m-phenylene PGI2 derivatives represented by Formula (I), preferred are those wherein R^1, Y, E and A represent the same meanings as described above, B is

(i)



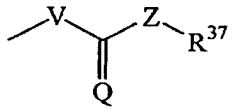
wherein V, Q, R^{29} and Z is the following in the definition of claim 2, the two R^{29}s may be the same or different, R^{37} is C_3-C_{12} cycloalkyl, C_4-C_{13} cycloalkylalkyl, C_3-C_{12} cycloalkyl substituted with 1 to 4 R^{38}s (wherein R^{38} is hydrogen or C_1-C_5 alkyl), C_4-C_{13} cycloalkylalkyl substituted with 1 to 3 R^{38}s (wherein R^{38} is defined as the same as the above), phenyl, substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl in claim 2), α-naphthyl, β-naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, α-furyl, β-furyl, α-thienyl or β-thienyl,

(ii)



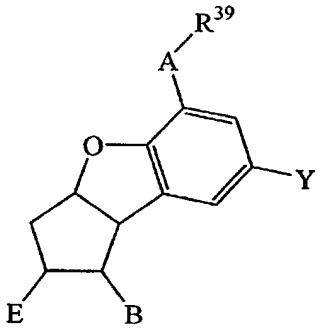
wherein Q, R^{29}, Z and R^{37} are defined as the same as the above, and the two R^{29}s may be the same or different, or

(iii)



wherein V, Q, Z and R^{37} are defined as the same as the above.

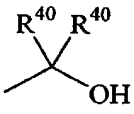
Among these, especially preferred are those represented by the following Formula (II):



(II)

[wherein R^{39} is

(i)

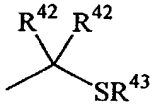


wherein R^{40} is hydrogen, C_1-C_4 linear alkyl or trifluoromethyl, the two R^{40} may be the same or different,

(ii) $-COOR^{41}$

wherein R^{41} is hydrogen, a pharmacologically acceptable cation or C_1-C_{12} linear alkyl,

(iii)

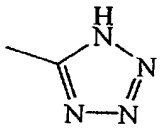


wherein R^{42} is hydrogen, C_1-C_4 linear alkyl or trifluoromethyl, the two R^{42}s may be the same or different, R^{43} is hydrogen, C_1-C_4 linear alkyl, phenyl, or $-C(=O)-R^{44}$ wherein R^{44} represents C_1-C_4 linear alkyl,

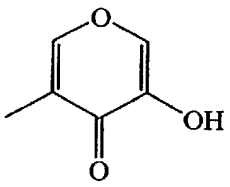
(iv) $-CH_2-R^{45}$

wherein R^{45} is

(1)

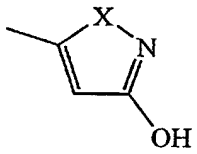


(2)



or

(3)

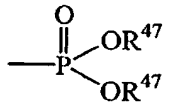


wherein X is the following in the definition of claim 2,

(v) $-C(R^{46})_3$

wherein R^{46} is hydrogen, fluorine, cyano or C_1-C_4 alkyl, and all R^{46}s may be the same or different,

(vi)



wherein R^{47} is hydrogen, C_1-C_4 alkyl, or a pharmacologically acceptable cation, and the two R^{47}s may be the same or different, or

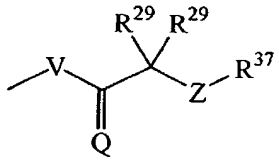
(vii) $-N(R^{48})_2$

wherein R^{48} is hydrogen, $-C(=O)-R^{49}$ or $-SO_2-R^{49}$ wherein R^{49} is C_1-C_4 linear alkyl or phenyl, and the two R^{48}s may be the same or different (when one of R^{48}s is $-SO_2-R^{49}$, the other R^{48} is not $-SO_2-R^{49}$),

Y is hydrogen, fluorine, chlorine or bromine,

B is

(i)



wherein V is

(1) $-CH_2CH_2-$,

(2) $-C\equiv C-$,

or

(3) $-CH=CH-$,

Q is

(1) =O,

(2)

$—R^{50}$
$—OR^{33}$

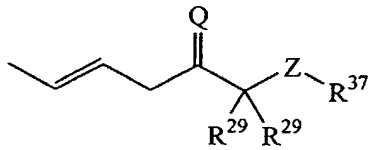
or

(3)

$—R^{50}$
$—R^{50}$

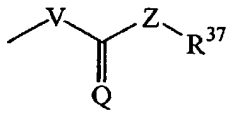
wherein R^{50} is hydrogen, C_1-C_4 linear alkyl, C_3 or C_4 branched alkyl, or trifluoromethyl, R^{33} represents the following in the definition of claim 2, the two R^{50}s may be the same or different, R^{29} represents the following in the definition of claim 2, and the two R^{29}s may be the same or different, Z represents the following in the definition of claim 2, and R^{37} represents the following in the definition of claim 3,

(ii)



wherein Q, R^{29}, Z and R^{37} are defined as the same as the above, and the two R^{29}s may be the same or different, or

(iii)

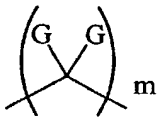


wherein V, Q, Z and R^{37} are defined as the same as the above,

E represents the following in the definition of claim 2,

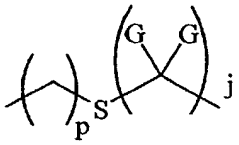
A is

(i)



wherein m is an integer of 0 to 3, G is hydrogen, fluorine, chlorine, bromine, iodine, trifluoromethyl or C_1-C_4 linear alkyl, and all Gs may be the same or different,

(ii)



wherein j is an integer of 1 or 2, p represents the following in the definition of claim 2, G is defined as the same as the above, and all Gs may be the same or different,

(iii) $-CH=CH-CH_2-$,

(iv) $-CH_2-CH=CH-$,

(v) $-CH_2-O-CH_2-$,

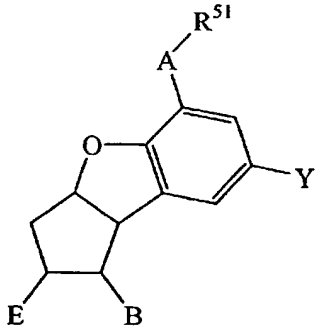
(vi) $-O-CH_2-$,

(vii) $-C\equiv C-$

or

(viii) -C=C- (trans)].

More preferred are those represented by the following Formula (III):



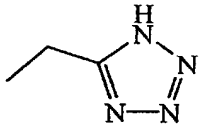
(III)

[wherein R^{51} is

(i) $-COOR^{52}$

wherein R^{52} is hydrogen, a pharmacologically acceptable cation or methyl, or

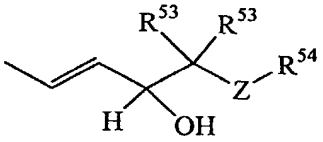
(ii)



wherein Y is hydrogen or fluorine,

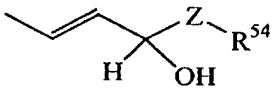
B is

(i)



wherein R^{53} is hydrogen, fluorine or C_1-C_4 alkyl, the two R^{53}s may be the same or different, Z represents the following in the definition of claim 2, R^{54} is C_5-C_7 cycloalkyl, phenyl, or substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl in claim 2), or

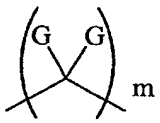
(ii)



wherein Z and R^{54} are defined as the same as the above,

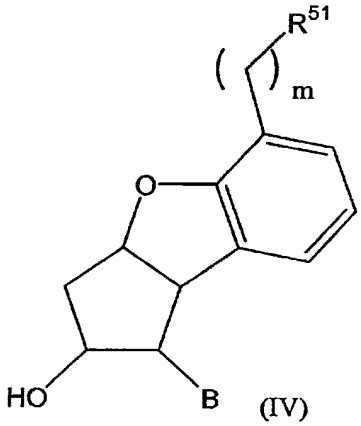
E is hydrogen or -OH,

A is



wherein m is an integer of 0 to 2, G represents hydrogen or fluorine, and all Gs may be the same or different].

Still more preferred are those represented by the following Formula (IV):

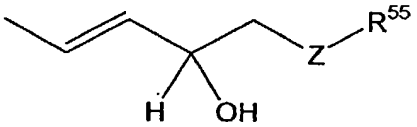


(IV)

[wherein R^{51} is the same meaning as described above,

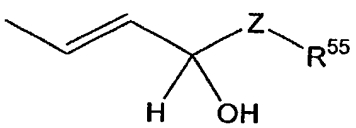
B is

(i)



wherein Z is the following in the definition of claim 2, R^{55} is C_5-C_7 cycloalkyl or phenyl, or

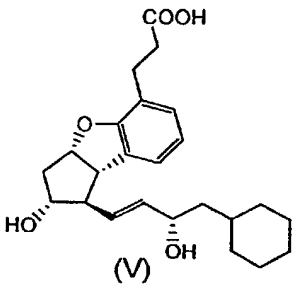
(ii)



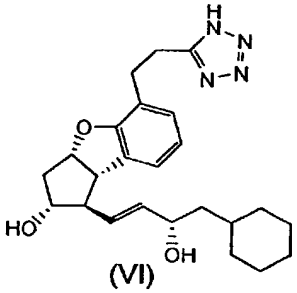
wherein Z and R^{55} are defined as the same as the above, m represents an integer of

0 to 2].

Among these, especially preferred are the compounds represented by the following Formula (V) or (VI):

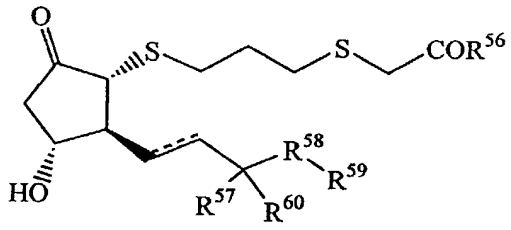


(V)



(VI)

Examples of the prostaglandin EP4 ligand of the present invention also include 3,7-dithiaprostanoic acid derivatives and azole derivatives. Examples of these include 3,7-dithiaprostanoic acid derivatives of the following Formula (VII), mixtures thereof with 8-epi compounds which are equilibrium compounds thereof, pharmacologically acceptable salts thereof, and clathrate compounds thereof included in cyclodextrin:



(VII)

[wherein R^{56} is hydroxy, C_1-C_6 alkyloxy or $NR^{61}R^{62}$ (wherein R^{61} and R^{62} independently represent hydrogen or C_1-C_6 alkyl),

R^{57} is hydrogen or hydroxy,

R^{58} is a single bond or C_1-C_6 alkylene,

R^{59} is

(1) C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl,

(2) C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl, each of which is substituted

with 1 to 3 C_1-C_6 alkyloxy or halogen,

(3) C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl, each of which is substituted with phenyl or C_3-C_7 cycloalkyl,

(4) phenyl, phenyloxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy,

(5) furyl, furyloxy, thienyl, thienyloxy, naphthyl, naphthyloxy, phthalanyl or phthalanyloxy,

(6) phenyl, phenyloxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy, each of which is substituted with 1 to 3 of the following groups:

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkyloxy, C_1-C_6 alkyl substituted with C_1-C_6 alkyloxy, C_1-C_6 alkyloxy substituted with C_1-C_6 alkyloxy, C_1-C_6 alkyl substituted with C_2-C_6 alkenyloxy, C_1-C_6 alkyl substituted with 1 to 3 hydroxy, C_1-C_6 alkyl substituted with 1 to 3 halogen, C_1-C_6 alkylthio, C_1-C_6 alkyl substituted with C_1-C_6 alkylthio, C_1-C_6 alkyloxy substituted with C_1-C_6 alkylthio, C_1-C_6 alkyl substituted with C_2-C_6 alkenylthio, C_1-C_6 alkylsulfonyl, halogen, trihalomethyl, cyano, nitro, amino, hydroxy, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyloxy, C_1-C_6 alkyl substituted with C_3-C_7 cycloalkyl, C_1-C_6 alkyl substituted with C_3-C_7 cycloalkyloxy, phenyl, phenyloxy, C_1-C_6 alkyl substituted with phenyl, C_2-C_6 alkenyl substituted with phenyl, C_2-C_6 alkynyl substituted with phenyl, C_1-C_6 alkyl substituted with phenyloxy, C_2-C_6 alkenyl substituted with phenyloxy, C_2-C_6 alkynyl substituted with phenyloxy, furyl, furyloxy, C_1-C_6 alkyl substituted with furyl, C_1-C_6 alkyl substituted with furyloxy, thienyl, thienyloxy, C_1-C_6 alkyl substituted with thienyl, or C_1-C_6 alkyl substituted with thienyloxy (provided that the above-mentioned phenyl, furyl, thienyl and cycloalkyl may be substiuted with 1 to 3 C_1-C_6 alkyl, C_1-C_6 alkyloxy, C_1-C_6 alkyl substituted with C_1-C_6 alkyloxy, nitro, halogen, trihalomethyl, amino, or hydroxy), or

(7) furyl, furyloxy, thienyl, thienyloxy, naphthyl, naphthyloxy, phthalanyl or phthalanyloxy substituted with 1 to 3 of the following groups:

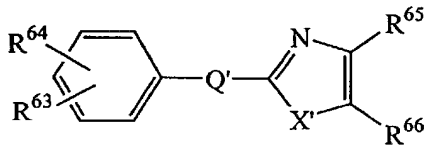
C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkyloxy, C_1-C_6 alkyl substituted with C_1-C_6 alkyloxy, C_1-C_6 alkyloxy substituted with C_1-C_6 alkyloxy, C_1-C_6 alkyl substituted with C_2-C_6 alkenyloxy, C_1-C_6 alkyl substituted with 1 to 3 hydroxy, C_1-C_6 alkyl substituted with 1 to 3 halogen, C_1-C_6 alkylthio, C_1-C_6 alkyl substituted with C_1-C_6 alkylthio, C_1-C_6 alkyloxy substituted with C_1-C_6 alkylthio, C_1-C_6 alkyl substituted with C_2-C_6 alkenylthio, C_1-C_6 alkylsulfonyl, halogen, trihalomethyl, cyano, nitro, amino, hydroxy, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyloxy, C_1-C_6 alkyl substituted with C_3-C_7 cycloalkyl, C_1-C_6 alkyl substituted with C_3-C_7 cycloalkyloxy, phenyl, phenyloxy, C_1-C_6 alkyl substituted with phenyl, C_2-C_6 alkenyl substituted with phenyl, C_2-C_6 alkynyl substituted with phenyl, C_1-C_6 alkyl substituted with phenyloxy, C_2-C_6 alkenyl substituted with phenyloxy, C_2-C_6 alkynyl substituted with phenyloxy, furyl, furyloxy, C_1-C_6 alkyl substituted with furyl, C_1-C_6 alkyl substituted with furyloxy, thienyl, thienyloxy, C_1-C_6 alkyl substituted with thienyl, or C_1-C_6 alkyl substituted with thienyloxy (provided that the above-mentioned phenyl, furyl, thienyl and cycloalkyl may be substiuted with 1 to 3 C_1-C_6 alkyl, C_1-C_6 alkyloxy, C_1-C_6 alkyl substituted with C_1-C_6 alkyloxy, nitro, halogen, trihalomethyl, amino, or hydroxy),

R^{60} is hydrogen or C_1-C_6 alkyl,

the symbol

is double bond or single bond, with the proviso that when R^{57} is hydrogen, the C_1-C_6 alkylene represented by R^{58} may be substituted with one hydroxy],

and also include the azole derivatives of the following Formula (VIII) and pharmacologically acceptable salts thereof:



(VIII)

[wherein R^{63} is

(1) C_1-C_6 alkyl substituted with hydroxy, protected carboxy or carboxy,

(2) carboxy,

(3) protected carboxy,

(4) carbamoyl,

(5) heterocyclic group,

(6) cyano,

(7) C_1-C_6 haloalkylsulfonyloxy,

(8) C_1-C_6 alkyloxy substituted with hydroxy or carbamoyl,

(9) aryl substituted with carboxy, protected carboxy, carbamoyl or heterocyclic group,

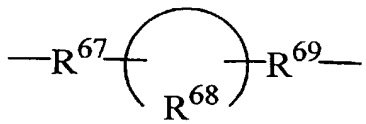
(10) amino which may be substituted with protected carboxy or C_1-C_6 alkylsulfonyl,

R^{64} represents hydrogen or C_1-C_6 alkyl,

R^{65} is aryl which may be substituted with halogen,

R^{66} is aryl which may be substituted with halogen,

Q is



(wherein -R^{67}- is single bond or C_1-C_6 alkylene,

is C_5-C_9 cycloalkene, C_3-C_9 cycloalkane, C_6-C_9 bicycloalkene or C_5-C_9

bicycloalkane,

$-R^{69}-$ is single bond or C_1-C_6 alkylene), and

X' is O, NH or S].

Here, the term "heterocyclic group" means saturated or unsaturated monocyclic or polycyclic group having at least one heteroatom selected from the group consisting of nitrogen, sulfur or oxygen; the term "protected carboxy" means (1) C_1-C_6 alkyl esters, (2) C_2-C_6 alkenyl esters, (3) C_2-C_6 alkynyl esters, (4) arylalkyl esters substituted with C_1-C_6 alkyl, C_1-C_6 alkyloxy, phenyl, nitro or halogen, or (5) aryl esters substituted with C_1-C_6 alkyl, C_1-C_6 alkyloxy, phenyl, nitro or halogen; and the term "aryl" means phenyl or naphthyl, which may be substituted with C_1-C_6 alkyl.

Among the compounds having binding activities for prostaglandin EP4 receptor, those having (an) asymmetric carbon(s) include various optical isomers, and those having at least two asymmetrical carbons include various diasteromers. The present invention include these optical isomers and respective isomers thereof. The present invention also include stereoisomers.

The compounds having binding activities for prostaglandin EP4 receptor and salts thereof *per se* are known, and may be produced by the methods described in the above-mentioned Laid-open patent application, International patent publications WO/8903387 and WO/0024727.

Examples of the pharmacologically acceptable salts include alkaline metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as calcium salt and magnesium salt; amine salts such as methylamine salt, dimethylamine salt, trimethylamine salt, methylpiperidine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt and lysine salt; ammonium salt; basic amino acid salts; inorganic acid salts such as hydrochloric acid salt and sulfuric acid salt; organic carboxylic acid salts such as acetic acid salt, tartaric acid salt and maleic acid salt; and organic sulfonic acid salts such as p-toluenesulfonic acid salt. However,

the pharmacologically acceptable salts are not restricted to those described above.

In application of the agent for modulating growth or generation of hair according to the present invention, one or several prostaglandin EP4 receptor ligands or (a) salt(s) thereof may be applied to head as it is, or the ligand(s) may be applied after being admixed with a vehicle, stablizer and/or the like, which are usually used in formulation of pharmaceuticals. Examples of such an additive include animal oils; plant oils; paraffin; gum arabic; saccharides such as starch, lactose, sucrose, glucose, dextrin and mannitol; inorganic acid salts such as calcium carbonate and calcium sulfate; organic acid salts such as sodium citrate, sodium lactate and magnesium stearate; water-soluble polymers such as methylcellulose, gelatin, polyethylene glycol, polyvinyl alcohol, polyvinylpyrrolidone, hydroxyethylcellulose and hydroxypropylcellulose; alcohols such as ethanol, glycerin, propylene glycol and sorbitol; and surfactants such as sorbitan aliphatic acid esters, polyoxyethylenesorbitan aliphatic acid esters, polyoxyethylene aliphatic acid esters and glycerin aliphatic acid esters. However, the additives are not restricted to those described above.

The agent for modulating growth or generation of hair according to the present invention may be applied in various dosage forms. More particularly, the agent may be in a form which is usually used, such as in the form of liquid, jelly, emulsion, aerosol or ointment. For example, it may be used as a hair-growing agent, hair tonic, hair liquid, hair lotion, hair cream, hair gel, hair foam, hair mist, hair oil, hair treatment, mousse, shampoo or rinse. Alternatively, it may be used as an injection solution for subcutaneous, intravenous or local injections. Further, it may be formulated into a dosage form for oral administration, such as tablets, powder, granules, balls and capsules. However, the formulations are not restricted to those described above.

As will be concretely shown in the Examples below, since the agent for

modulating growth or generation of hair according to the present invention has a high selectivity to EP4 receptor subtype and exhibits hair-growing or hair-generating activities to epilated rabbit models of different ages (17 and 8 weeks old), it may be used for therapy or treatment of, for example, atrichia and hirsutism, or alopecia (male pattern alopecia and alopecia areata) as abnormal hair growth.

The dose of administration of the agent for modulating growth or generation of hair according to the present invention varies depending on the symptom, age, individual difference, formulation of the agent and the like, and usually the agent may be administered in an amount of 0.0001 mg to 1000 mg, preferably 0.001 mg to 100 mg in one time or in several times. However, the dose of administration is not restricted thereto.

The agent for modulating growth or generation of hair according to the present invention may be administered together with (a) hair-growing agent(s) (blood circulation promoters, potassium channel openers, androgen inhibitors, antiinflammatory agents, follicle-stimulators, antioxidants and keratolytic drugs) other than the agent of the present invention simultaneously or with a time interval. Examples of the hair-growing agents which may be used together with the agent for modulating growth or generation of hair according to the present invention include blood circulation promoters such as carpronium hydrochloride, cepharanthin and nicotinamide; potassium channel openers such as minoxidil, pinacidil and carpronium hydrochloride; androgen inhibitors such as 5α reductase inhibitors such as finasteride, and eugenyl glucoside; antiinflammatory agents such as glycyrrhizic acid and derivatives thereof, and glycyrrhetinic acid and derivatives thereof; follicle stimulators such as pentadecanoic acid glyceride, carpronium hydrochloride and procyanidin B; antioxidants such as vitamins including vitamin C, vitamin E and derivatives thereof; keratolytic agents such as aspirin; hormones such as estrogen and adenocorticotropic hormone; and amino acids such as taurine.

The agent for modulating growth or generation of hair according to the present invention may also be administered to animals other than human. That is, the agent can modulate growth or generation of hair by administering it to animals other than human, so that it can be applied for epilation and abnormality of fur, or therapy or treatment of animals other than human.

Examples

To describe the present invention in more detail, examples thereof will now be described.

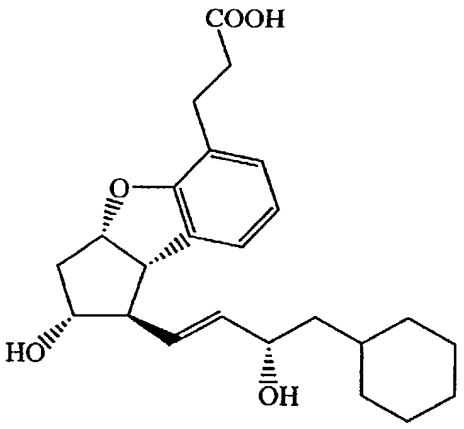
Example 1

Receptor Binding Experiment Using PGE_2 Receptor Subtype-expressing Cells

The compound of the Formula (I) described above was tested for its selective binding activity to EP4 receptor by using PGE_2 receptor subtype-expressing cells.

According to the reported method (Breyer,R.M. et al.,J.Biol.Chem.269,6163-6169(1994)), cloned human PGE_2 receptor subtypes (EP3 and EP4) were transiently expressed by COS-7 cells. EP2 was stably expressed by CHO cells. These cells were prepared into membrane specimens. Each of the prepared membrane fractions (10 μg/tube) was incubated with a reaction solution containing ^{3}H-PGE_2 at 30°C for 1 hour. The reaction was terminated by iced buffer (10mM MES(pH6.0), 10mM $MgCl_2$, 1mM EDTA), and the resultant was subjected to filtration by means of suction under reduced pressure to trap the bound ^{3}H-PGE_2 on a glass filter (GF/C), followed by measurement of the radioactivity with a liquid scintillation counter.

The Kd value was determined from Scatchard plot according to the conventional method. Non-specific binding was determined in terms of the amount of bound radioactivity in the presence of an excess amount (5 μM) of non-labeled PGE_2. Measurement of inhibition of ^{3}H-PGE_2 binding by Compound 1 was carried out by adding ^{3}H-PGE_2 (5 nM) and various concentrations of Compound 1 of the following Formula (V):



(V)

Compound 1 was prepared according to Example 17 of Japanese Patent No. 1933167.

The dissociation constant Ki (nM) of Compound 1 was calculated according to the following equation:

$Ki=IC_{50}/(1+([C]/Kd))$

As a result, the dissociation constant Ki of Compound 1 to EP4 was 19 nM. Thus, Compound 1 has a high selectivity to EP4 receptor subtype and its binding abilities to other receptor subtypes are low, so that it is thought that its side effect is small when it is administered.

Example 2

Hair-growing or Hair-generating Action

To investigate the hair-growth or hair-generation modulation action of Compound 1 which was shown to be a prostaglandin EP4 receptor agonist in Example 1, hair-growth/generation test was performed using rabbits. The test was carried out as follows. The hair on the back of each rabbit was removed with an electric clipper and evacream was applied for a short time to the back so as to epilate the back. After wiping the epilated region with water, test compound was subcutaneously administered to the back at a dose of 0.25 ml/kg (dissolved in 0.9%

sodium chloride solution) once a day from the second day to 20th day after epilation. The state of generation of hair was observed and the length of the hair was measured.

As a result, generation of hair was observed on the 15th day after administration of Compound 1, and the hair-generated area became not less than 50% in 3 rabbits out of 4 rabbits on the 20th day after administration. Further, the length of the new hair was increased by administration of Compound 1. The results are shown in Table 1. From these results, it was proved that Compound 1 has excellent hair-growing or hair-genrating activity.

Table 1

Hair-Growth or Hair-Generation Modulation Activity of Compound 1 (20th day)

	Rate of Hair-generated Area		Length of New Hair
	(%)	Rate of Rabbits with 50% or More Hair-Generated Area	(mm)
Control Group	10.0±5.5	0/4	4.8±0.4
Compound 1-administered Group			
0.03mg/kg	15.8±13.2	1/4	6.0±0.6
0.1mg/kg	48.8±13.6	3/4	7.3±0.5*

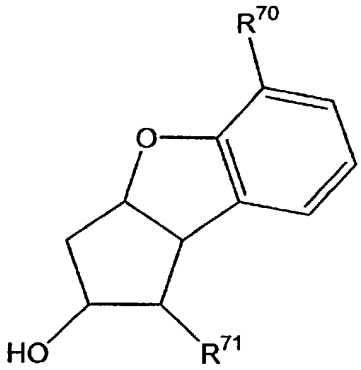
Values indicate mean ± standard error. *: $p<0.05$ vs. control group (Dunnett's t-test)

Example 3

Magnus Experiment Using Rabbit Saphenous Vein

Investigation of agonistic activity to EP4 was carried out by an improved method of the method of Lydford et al. (S. J. Lydford et al., Br. J. Pharmacol. 117, 13-20 (1996)) using rabbit saphenous veins. That is, each rabbit was deeply anesthetized by administering pentobarbital (50 mg/kg) to auricular vein, and then sacrificed by bleeding by cutting carotid artery. Saphenous vein was carefully but quickly removed and transferred into Krebs solution (NaCl 118.1 mM, KCl 5.31 mM, $MgSO_4$ 1.01 mM, $CaCl_2$ 3.52 mM, NaH_2PO_4 1.09 mM, $NaHCO_3$ 25.0 mM, glucose

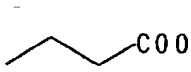
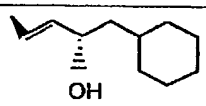
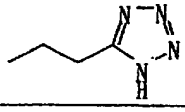
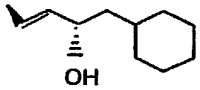
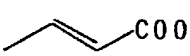
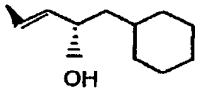
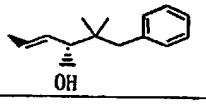
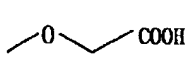
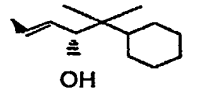
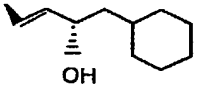
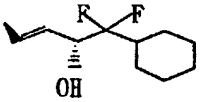
9.99 mM, pH 7.4) which was preliminarily saturated with 95% O_2 + 5% CO_2 mixed gas. The connective tissue and the fatty tissue of each saphenous vein were isolated using a scissors for ophthalmology to prepare a ring preparation with a width of about 4 mm. This ring preparation was mounted on a hook for blood vessels, and then suspended in a Magnus tube filled with Krebs solution aerated with 95% O_2 + 5% CO_2 mixed gas and kept at 37°C. The isometric tension of each blood vessel was recorded on a recorder through an isometric transducer. To each blood vessel, a base tension of 1.0 g was applied and the blood vessel tissue was stabilized for about 30 minutes until the baseline became stabilized. After the baseline became stable, the blood vessel was contracted with 40 mM KCl, and the shrinkage and washing were repeated until the contraction became stable. After the contraction with KCl became stable, a thromboxane antagonist S-145 (1000 nM) was applied previously and then cumulative application experiments of Compounds 1 to 7 were carried out. More specifically, the reactivity to PGE_2 which was a positive control drug was measured, and after washing, the action of each compound was studied. The effectiveness of each drug was expressed in terms of the concentration (EC_{50}) at which the rate of relaxation of the test drug to the contraction by 40 mM KCl was 50%. EC_{50} value was calculated by plotting logarithm of the concentration of each drug along the abscissa and plotting the rate of relaxation with respect to the contraction by 40 mM KCl along the ordinate, and by determining the concentration at which the height of contraction was 50% based on the linear area of the concentration-reaction curve in each experiment.



Compounds 2, 6 and 7 were prepared as described in International Publication WO/0024727, Compound 3 was prepared as described in Japanese Patent No. 2893812, Compound 4 was prepared as described in Japanese Patent No. 1933167, and Compound 5 was prepared as described in Japanese Patent No. 1974492.

The results are shown in Table 2. Thus, Compounds 1 to 7 have high selectivities to EP4 receptor subtype and their binding abilities to other receptor subtypes are low, so that that their side effects are thought to be small when they are administered.

Table 2 Agonistic Activity of Compounds to EP4 Receptor in Rabbit Saphenous Vein Relaxation Reaction

Compound	R^{70}	R^{71}	EC_{50} (nM)
1			6
2			3
3			6
4			7
5			26
6			33
7			2

Example 4

Hair-growing or Hair-generating Action

To investigate the hair-growth or hair-generation modulation action of Compound 2 which was shown to be a prostaglandin EP4 receptor agonist in Example 3, hair-growth/generation test was performed using young rabbits (New Zealand White rabbits, male, 8 weeks old, Kitayama Labes). The test was carried out as follows. The hair on the back of each rabbit was removed and evacream was applied for a short time to the back so as to epilate the back. After wiping the epilated region with water, test compound was subcutaneously administered to the

back at a dose of 0.25 ml/kg once a day from the second day to 7th day after epilation. The length of the hair was measured.

As a result, the length of the new hair was increased. The results are shown in Table 2. By these results, it was proved that Compound 2 has an excellent hair-growing or hair-generating activity.

Table 3

Hair-Growth or Hair-Generation Modulation Activity of Compound 1 (7th day)

	Length of New Hair (mm)
Control Group	9.2±0.3
Compound 2-administered Group 0.03mg/kg	11.7±0.5*

Values indicate mean ± standard error. *: $p<0.05$ vs. control group (Student's t-test)

Industrial Availability

The agent for modulating growth or generation of hair according to the present invention has an excellent activity to modulate growth or generation of hair, and its side effects are small. Therefore, it is useful for therapy or treatment of atrichia and hirsutism, or alopecia (male pattern alopecia and alopecia areata) as abnormal hair growth.